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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/802,417	DURING ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *5,6,17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-16 and 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/14/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed May 16, 2008 (hereinafter referred to as "the response") has been entered. Claims 1 and 13 were amended and Claims 22 and 23 were newly added.

Accordingly, Claims 1-23 remain pending in the instant application.

Applicants elected the species adeno-associated viral vector and subthalamic nucleus (STN) for prosecution on the merits.

Claims 5, 6, 17, and 18 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on December 13, 2006.

Accordingly, Claims 1-4, 7-16, and 19-23 are examined herein.

The rejection of Claims 1-3, 7-16, and 19-21 under 35 U.S.C. 103(a), as being unpatentable over Robert et al. (1997, Gene Therapy 4: 1237-1245, cited on IDS filed 3/16/04), is **withdrawn** in view of the amendments to the claims and the arguments set forth at pages 10-12 of the response.

The rejection of Claims 1-4, 7-16, and 19-21 under 35 U.S.C. 103(a), as being unpatentable over Robert et al. (1997, Gene Therapy 4: 1237-1245) and USPN 6,180,613 (Kaplitt et al., filed June 6, 1995), is **withdrawn** in view of the amendments to the claims and the arguments set forth at pages 10-12 of the response.

Claim Objections

Claims 1-4, 7-16, and 19-21 stand objected to and Claims 22 and 23 are objected to for encompassing non-elected subject matter. In view of the rejections of the generic claims, non-elected species should be deleted from the claims. Following an election of species requirement, when no generic

claim is finally held to be allowable, the claims are restricted to the elected species. Appropriate correction is required.

At page 6 of the response, Applicants allege that amended Claims 1 and 13 are generic and allowable. On the contrary, the claims remain rejected for the reasons set forth hereinbelow.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 7-16, and 19-21 stand rejected and Claims 22 and 23 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-14 of U.S. Patent No. 6,780,409. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims recite the identical steps as the present claims, with the only difference being that the patented claims are directed to treating Parkinson's disease, whereas the present

claims are more broadly drawn to expressing GAD in a subject without requiring any therapeutic result. Thus, the patented claims anticipate the present claims (anticipation analysis).

At page 6 of the response, Applicants note that they will file the appropriate terminal disclaimer once allowable subject matter is found.

Accordingly, the rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-4, 7-16, and 19-21 stand rejected and Claims 22 and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating Parkinson's disease by administering to a region of the brain a vector comprising a nucleotide sequence encoding glutamic acid decarboxylase (GAD), wherein a symptom of Parkinson's disease is ameliorated, does not reasonably provide enablement for the use of any type of vector for the treatment of any disease, nor for any target tissue other than the brain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are set forth in *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the relative level of skill of those in the art, (4) the predictability of the art, (5) the breadth of the

claims, (6) the amount of direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary (MPEP 2164.01(a)).

Nature of the invention and breadth of the claims. The claims are directed to a method for altering expression of glutamic acid decarboxylase (GAD) in a region of the central nervous system (CNS) of a subject by delivering a vector comprising a nucleotide sequence encoding GAD to a target site in the CNS and expressing GAD in the target site. The claims are further directed to a method for altering expression of GAD in a region of the CNS of a subject having a disorder which causes morphological and/or functional abnormality of a neural cell or population of neural cells by delivering a vector encoding GAD to a target site in the CNS and expressing GAD in the target site. The claims specifically recite delivering the vector to a subject having a neurodegenerative disorder, including Parkinson's disease. The claims cover therapeutic as well as non-therapeutic protocols. Thus, the claims encompass gene therapy. The claims encompass the use of any type of vector comprising a GAD gene, with any promoter driving expression of the gene, any route of administration, to any subject, and administration to any region of the CNS, with some claims reciting specific regions of the brain. The specification contemplates using a wide variety of vectors to achieve a therapeutic effect, including viral vectors and non-viral vectors. It is well-established that the specification must teach how to use the claimed method over the full scope. However, the instant specification fails to provide specific guidance teaching one of skill in the art how to use the claimed method to treat the wide variety of diseases encompassed by the claims. Furthermore, the specification does not assert any utility for non-therapeutic gene delivery.

Amount of direction or guidance presented and presence or absence of working examples.

The specification fails to provide an enabling disclosure for methods of treating a wide variety of diseases, including Parkinson's disease using the broad scope of vectors contemplated, with any route of administration, to any region of the CNS, because the specification does not adequately teach how to use the claimed methods over such a broad scope to produce a therapeutic effect. The specification provides

working examples demonstrating that administration of an rAAV vector encoding GAD significantly improves clinical deficits associated with Parkinson's disease in an animal model (the 6-OHDA lesion model). However, the specification does not provide specific guidance with regard to the treatment of other diseases or for the use of other types of vectors for treating those diseases. With regard to the use of other types of vectors, the specification only provides general guidance. In an unpredictable art, specific guidance rather than general guidance is required. For the reasons discussed herein below, the gene therapy art is highly unpredictable.

State of the prior art and level of predictability in the art. The specification fails to provide an enabling disclosure teaching how to use the broad scope of vectors covered in the claims therapeutically for the reasons that following. While non-therapeutic gene delivery and expression in experimental animal models is relatively routine, the development of therapeutic protocols is not, with intensive investigation leading to only limited success.

Gene therapy is not routinely successful. Therefore, the disclosure itself must provide the necessary teachings with regard to how to carry out the claimed method to achieve a therapeutic effect. At the time the application was filed, the art of administering any type of genetic expression vector to an individual so as to provide a tangible therapeutic benefit was poorly developed and unpredictable. The NIH ad hoc committee to assess the current status and promise of gene therapy reported in December 1995 that "clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims...," and that "significant problems remain in all basic aspects of gene therapy" (Orkin and Motulsky, p. 1). Orkin and Motulsky also point out that "[t]he types of diseases under consideration for gene therapy are diverse; hence, many different treatment strategies are being investigated, each with its own set of scientific and clinical challenges" (page 1, paragraph 2). In a review article published in Scientific American in June 1997, Theodore Friedmann discusses the technical barriers which have so far prevented successful gene therapy, and states "So far, however, no approach

has definitively improved the health of a single one of the more than 2,000 patients who have enrolled in gene therapy trials worldwide" (p. 96). In a review article published in Nature in September 1997, Inder Verma states "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (p. 239). The instant specification does not adequately teach one skilled in the art how to use vectors other than rAAV vectors to achieve a therapeutic effect in the treatment of diseases other than Parkinson's disease. Thus, absent evidence that the claimed methods can be used over the full scope in gene therapy applications to produce a therapeutic effect in an immunocompetent animal, such as a human or appropriate animal model, claims that encompass the use of any GAD vector, for the treatment of diseases other than Parkinson's disease, are not enabled by the disclosure.

The specification fails to provide an enabling disclosure for targeting appropriate cells for the treatment of the diseases referred to in the specification. The specification contemplates using a wide variety of types of vectors. Only general guidance is offered with regard to delivering vectors other than rAAV to an appropriate site. However, the art recognizes that targeting strategies are not currently sufficient to overcome the problems known in the art. More importantly, the disclosure does not offer a solution to this problem. While progress has been made in recent years for *in vivo* gene transfer, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings in the art. For example, Miller et al. (1995) review the types of vectors available for *in vivo* gene therapy, and conclude that "for long-term success as well as the widespread applicability of human gene therapy, there will have to be advances … targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain et al. (1998) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph).

Deonarain et al. review new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (1997) review vectors known in the art for use in gene therapy and discuss problems associated with each type of vector. The teachings of Verma et al. indicate that a resolution to vector targeting has not been achieved in the art (see entire article). Verma et al. also teach that appropriate regulatory elements may improve expression, but that it is unpredictable which tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal et al. (1995) also review various vectors known in the art and indicate that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

In an article published after the effective filing date of the instant application, Rubanyi (2001) teaches that the problems described above remain unsolved at the time the instant application was filed. Rubanyi states, "[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far …" (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see especially the section under "3. Technical hurdles to be overcome in the future", pp. 116-125).

Beyond the technical barriers to all gene therapy approaches, each disease to be treated using gene therapy presents a unique set of challenges that must be addressed individually. The claimed methods encompass the use of a wide variety of vector types to treat any disease. While other vector types may prove useful in the treatment of other diseases, their uses may be limited by the specific effects sought to be achieved. Rubanyi teaches, "each disease indication has its specific technical hurdles to overcome before gene therapy can become successful in the clinic (p. 131, paragraph 4). Rubanyi states,

"the most promising areas for gene therapy today are hemophilias, for monogenic diseases, and cardiovascular disease (more specifically, therapeutic angiogenesis for myocardial ischemia and peripheral vascular disease…) among multigenic diseases" (p. 113, paragraph 4). As of the filing date of the instant application however, even the most promising areas presented barriers to successful gene therapy that could not be overcome by routine experimentation.

The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al., p. 1789, column 1, paragraph 1). Rather, the prior art shows that intensive investigation has met with limited success.

Even as late as 2003, those of skill in the art recognized that substantial hurdles remained in the development of gene therapy protocols. Thomas et al. (2003) state that "[a]s more work is needed to develop site-specific integrating vectors, more work is also needed to improve the ability of vectors to home in on and infect specific target-cell populations" (page 356, column 1, paragraph 2).

Relative level of skill of those in the art and quantity of experimentation necessary. Although the level of skill in the art is high, given the high degree of unpredictability in the gene therapy art, the skilled artisan would be required to engage in intensive investigation, rather than routine experimentation to develop a therapeutic protocol using any GAD vector for the treatment of any disease of the CNS. In view of the quantity of experimentation necessary to determine appropriate parameters for using the claimed methods therapeutically, and given the limited applicable working examples demonstrating an *in vivo* therapeutic effect for Parkinson's disease, the limited guidance in the specification, the broad scope of the claims with regard to the vectors and tissue targets, and the unpredictability in the gene therapy art, undue experimentation would have been required for one skilled in the art to practice the claimed methods over the full scope.

At pages 6-9 of the response, Applicants argue that the claimed invention is fully enabled. Applicants' arguments rely on the 37 CFR 1.132 Declaration of Dr. Kaplitt. The declaration has been

fully considered but is not found to be persuasive because the declaration relies on evidence that is not of record. The declaration cites Exhibits A-F, but none of the exhibits were provided. The Examiner cannot comment on evidence that is not of record.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 7-16, and 19-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4, 7-16, and 19-23 are indefinite in their recitation of "glutamic acid decarboxylase (GAD_{65})" at lines 1-2 of Claims 1 and 13 and at lines 6-7 of Claim 13 because it is unclear whether the limitations in parentheses are part of the claimed invention or merely exemplary. See MPEP § 2173.05(d). Recitation of "glutamic acid decarboxylase 65 (GAD_{65})" would be remedial.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, the claims recite the broad recitation "glutamic acid decarboxylase," and the claims also recite "GAD_{65}" which is the narrower

statement of the range/limitation. Recitation of "glutamic acid decarboxylase 65 (GAD_{65})" would be remedial.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk, Ph.D. whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

/Anne-Marie Falk/
Primary Examiner, Art Unit 1632